Comments on the Proposed Consent Decree Under the Clean Air Act and the Comprehensive Environmental Response, Compensation, and Liability Act

United States *v.* S.H. Bell Company
Civil Action No. 4:17-cv-131
D.J. Ref. No. 90-5-2-1-11688/1
82 Fed. Reg. 8,436 (Jan. 25, 2017)

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1 Introduction

Gradient is submitting the following comments on the proposed Consent Decree lodged with the United States District Court for the Northern District of Ohio in the lawsuit entitled *United States v. S.H. Bell Company*, Civil Action No. 4:17-cv-131 (D.J. Ref. No. 90-5-2-1-11688/1) ("Consent Decree") (US District Court, Northern District of Ohio, Eastern Division *et al*., 2017). The Consent Decree states that emissions of manganese (Mn) in East Liverpool, Ohio, "present an imminent and substantial endangerment to public health or welfare" (US District Court, Northern District of Ohio, Eastern Division *et al*., 2017). Gradient scientists have conducted several in-depth toxicological evaluations of Mn, including evaluations of Mn epidemiology, animal, and toxicokinetic studies. Gradient scientists published an article in 2009 that described a proposal for a revised reference concentration (RfC) for Mn (Bailey *et al*., 2009) based on a thorough review of the most recent Mn occupational studies and Mn toxicokinetic studies that describe Mn inhalation concentrations and corresponding levels of Mn in the brain relative to normal levels of Mn in the brain. We continue to follow scientific developments in the field of Mn toxicology and have conducted several in-depth updates to our evaluation of Mn toxicity and human health risk. Our overall comment in this matter is that the Consent Decree and associated Complaint (US DOJ, 2017) are inconsistent with the best available scientific evidence for human health risks from exposure to Mn, and, therefore, provide no scientific basis for the conclusion that Mn exposures in the East Liverpool community represent an imminent public health hazard.[1]

Our comments are detailed in the following sections.

[1] We note that Gradient has worked on projects involving air exposures to Mn for a number of private sector clients. The opinions expressed here are solely those of the authors.

2 Levels of Mn in East Liverpool, Ohio, Air Do Not Present a Human Health Hazard

The Consent Decree states that emissions of Mn in the East Liverpool, Ohio, area "present an imminent and substantial endangerment to public health or welfare" (US District Court, Northern District of Ohio, Eastern Division *et al*., 2017). We strongly disagree with this statement, as outlined in a recent letter we submitted to the Agency of Toxic Substances and Disease Registry (ATSDR) (Beck and Bailey, 2016), also attached in Appendix A. The following bullets are excerpted from this letter (Beck and Bailey, 2016):

- For evaluating potential human health risks from Mn in air, ATSDR should use only the Mn Minimal Risk Level (MRL), a value that is supported by the best available science, and not the outdated US EPA Mn reference concentration (RfC).
- ATSDR's comparison of total suspended particulate (TSP) Mn concentration data to the Mn MRL is not scientifically supported. Instead, ATSDR should have used the more biologically appropriate respirable or PM_{10} (particulate matter with size mostly 10 microns or less)[2] Mn concentration data for comparison to the MRL.
- The Mn PM_{10} data available to date for East Liverpool, OH, suggest that Mn PM_{10} concentrations are only 20-35% of the Mn TSP air concentrations. Therefore, Mn TSP concentrations are not a reliable indicator of the more biologically appropriate respirable or PM_{10} Mn concentrations, and use of Mn TSP data results in a larger and incorrect estimate of Mn risk for the East Liverpool community than would be obtained from the Mn PM_{10} data. It is our understanding that ATSDR is aware of Mn PM_{10} data for East Liverpool for 2009 and of the difference in PM_{10} *vs*. TSP Mn concentrations, and we have been informed that they are also aware of 2016 Mn PM_{10} data; therefore, it is unclear why ATSDR used Mn TSP data instead of the more biologically relevant Mn PM_{10} data to evaluate Mn risk for the East Liverpool community.
- ATSDR's use of daily or average monthly Mn concentrations for comparison to the MRL is not scientifically supported. Instead, ATSDR should have only compared long-term chronic average Mn concentrations to the MRL.
- Our evaluation of more recent Mn PM_{10} data, and application of long-term average exposure concentrations, indicates there is no exceedance of the Mn MRL, and, therefore, no increased risk from Mn to the East Liverpool, OH, community.
- Two recent community studies incorrectly concluded, based on comparisons of Mn TSP data for East Liverpool, OH, *vs*. Marietta, OH, that there is a correlation between an increase in neurological deficits in the East Liverpool community and increased levels of Mn in air. However, comparison of the more biologically relevant Mn PM_{10} data to health indicators between these two towns does not provide reliable evidence for a correlation between neurological effects and levels of Mn in air in East Liverpool.
- Therefore, there is no scientific basis for ATSDR's conclusions that Mn exposures in the East Liverpool community represent a public health hazard and that such exposures should be mitigated as soon as possible to reduce harmful exposures.

[2] Note that PM_{10} is generally a conservative estimate of the concentration in the respirable PM_5 fraction.

3 The Monthly Response Action Levels Are Overly Conservative and Not Consistent with the Best Available Science

The Consent Decree (US District Court, Northern District of Ohio, Eastern Division *et al*., 2017) describes Response Action Levels for Mn as follows:

- **Preventative Action Levels (based on PM_{10} measurements)**:
  - Rolling annual average Mn concentration of 0.3 µg/m^3
  - Calendar monthly average of 0.57 µg/m^3
- **Exceptional Action Level (based on PM_{10} measurements):**
  - Calendar monthly average of 1.0 µg/m^3

The preventative annual rolling average target of 0.3 µg/m^3 is equal to the ATSDR Mn Minimal Risk Level (MRL) (ATSDR, 2012), which is based on chronic (long-term) exposures and, thus, seems reasonable. In contrast, the Mn monthly action levels are very conservative and not consistent with the available science regarding the potential toxicity from exposure to Mn in air, nor with an understanding of Mn homeostasis in the body (*i.e.*, since Mn essential nutrient, Mn levels are regulated by normal metabolic processes). We propose that an air concentration of 10 µg/m^3 as an average of daily measurements over a month would be health protective.

The following sections summarize our rationale for this proposal.

3.1 Consideration of Recent Mn PBPK Models

- A physiologically based pharmacokinetic (PBPK) Mn model (Schroeter *et al*., 2011) estimates Mn globus pallidus (a part of the brain that is a target of Mn toxicity) concentrations following different Mn inhalation concentrations. The model includes: (1) absorption of Mn into the bloodstream *via* inhalation, (2) uptake of Mn directly into the brain *via* the olfactory nerve/bulb following inhalation, and (3) dietary exposure to Mn (3 mg/day). The model indicates that Mn brain concentrations do not increase above normal levels (~0.4 µg/g) until inhalation concentrations exceed 10 µg/m^3.
  - The Schroeter *et al*. (2011) article (Figure 11) indicates that an inhalation concentration of 10 µg/m^3 over a 90-day exposure period "predicted no appreciable increase (<1%) in brain Mn concentrations above background levels that result from normal dietary exposure" over the entire 90-day period. The authors indicate that concentrations as high as 100 µg/m^3 result in only "slight increases (~5%) in brain Mn concentration above background levels" for all days during the 90-day exposure period (Schroeter *et al*., 2011).
  - These results suggest that because Mn is an essential nutrient, there is homeostatic control of Mn in the body and that Mn concentrations as high as 10 µg/m^3 are not likely to increase Mn

concentrations in the brain above normal levels (0.4 µg/g), even over long periods of time (*i.e.*, up to at least 90 days).

- Another PBPK model evaluated sensitive populations (*i.e.*, fetus, neonate, child) (Yoon *et al*., 2011) and found similar results for continuous Mn exposures. That is, the model indicates that Mn brain concentrations do not begin to increase above background levels (0.4 µg/g) in these sensitive populations until concentrations greater than continuous exposure to 10 µg/m^3. Note that while the study does show an increase in Mn levels in the brains of infants at exposure concentrations of 1 µg/m^3, this increase is within the range of normal Mn levels in the brain (*i.e.*, 0.3-0.4 µg/g). As the authors describe, this increase is likely because infants require Mn at this stage of development, and, therefore, increased uptake of Mn in the brain during this period is not unexpected.
- It should be emphasized that 10 µg/m^3 is not a neurological effect level. Schroeter *et al*. (2012) applied the Mn PBPK model (Schroeter *et al*., 2011) to identify a corresponding no effect level of 0.8 µg/g Mn in the primate brain, indicating that neurological effects are unlikely to occur until Mn brain concentrations are more than double the normal level of 0.4 µg/g.[3]
- Given that, based on the Schroeter *et al*. (2011) and Yoon *et al*. (2011) models, continuous exposure to 10 µg/m^3 Mn is not likely to increase Mn levels in the brain above normal (0.4 µg/g), an exposure concentration of 1.0 µg/m^3 (the Exceptional Action Level) would certainly not result in an increase in brain Mn concentrations. Based on an evaluation of the Schroeter *et al*. (2011) and Yoon *et al*. (2011) models, even a continuous exposure concentration of 100 µg/m^3 is only likely to increase Mn brain concentrations by a very small amount, resulting in a level consistent with a no observed effect level (NOEL) of 0.8 µg/g from Schroeter *et al*. (2012). This comparison emphasizes that a 10-fold increase in the Exceptional Action Level of 1 µg/m^3 to 10 µg/m^3 is health protective. A 10 µg/m^3 Exceptional Action Level is still be well below a level at which health effects would occur.
- Based on the available information summarized here, an Exceptional Action Level concentration of 100 µg/m^3 on a monthly basis would seem reasonable (or possibly 30 µg/m^3, see next section). However, one could add an uncertainty factor of 10 for an Exceptional Action Level of 10 µg/m^3. Note that 10 µg/m^3 is well above Mn respirable concentrations measured in East Liverpool, Ohio.

3.2 Consideration of a No Effect Level for Workers Applied by ATSDR to Derive the Mn MRL

- The respirable Mn BMDL$_{10}$ (95% lower confidence limit on the benchmark dose for a 10% extra risk compared to controls) derived by ATSDR for a worker population from the Roels *et al*. (1992) study is 142 µg/m^3. This Mn exposure concentration can be considered to be consistent with a no effect level (NOEL) for workers (*i.e.*, a point of departure from which to derive health-protective values).
- Adjusting the 142 µg/m^3 NOEL for workers to a continuous exposure concentration (24 hours per day, 7 days per week) results in a NOEL of 30 µg/m^3 respirable Mn for the general population. This value is consistent with the PBPK model (Schroeter *et al*., 2011) that shows Mn concentrations in the brain are not likely to increase until concentrations greater than 10 µg/m^3.

[3] For further context, the no adverse effect level in workers is 142 µg/m^3, comparable to 30 µg/m^3 in the general population. Exposures would have to exceed these levels for there to be a potential for adverse effects. Details on this point are provided in the next section.

- The PBPK model and the $BMDL_{10}$ value derived by ATSDR from the Roels *et al*. (1992) data suggest that an Exceptional Action Level of 10-30 µg/m^3 respirable Mn would be sufficiently health protective.

3.3 Consideration of Non-respirable Mn Particulates

As described in our letter to ATSDR (Beck and Bailey, 2016), the respirable Mn particulate fraction is the most biologically relevant form of Mn particulates, because this is the fraction that can penetrate to the deep lung and be absorbed systemically. In contrast, larger particulates are trapped in the upper airways (*i.e.*, the naso-pharyngeal passages), do not penetrate the lung tissue, and, thus, are not absorbed systemically. Below, we provide more information regarding the lack of potential risk from "non-respirable" Mn that does not deposit in the lung tissue.

- Only very small Mn particles (*i.e.*, less than 200 nanometers, or 0.2 micrometers[4]) can travel along the olfactory nerve to the brain (Elder *et al*., 2006). The Schroeter *et al*. (2011) and Yoon *et al*. (2011) PBPK models include the olfactory pathway to the brain for these very small Mn particles. Particles this small are contained within the PM_{10} fraction (*i.e.*, particulate matter with particle sizes that are 10 micrometers and smaller). Therefore, the only fraction that contains particles small enough to reach the brain is the PM_{10} fraction, and within that fraction, only those particles smaller than 200 nanometers can reach the brain. Studies that have evaluated the transport of Mn directly to the brain *via* the olfactory or trigeminal nerve have evaluated particle sizes of less than 10 micrometers (approximately 2-3 micrometers[5]) (*e.g.*, Brenneman *et al*., 2000; Lewis *et al*., 2005).
- Therefore, there is no evidence that larger, non-respirable particles (larger than PM_{10}) that deposit in the upper airways can reach the brain *via* olfactory nerve transport. Therefore, the only possible pathway for exposure to Mn particles larger than PM_{10} (*i.e.*, larger than 10 micrometers) is *via* ingestion following removal of Mn particulates from the respiratory tract *via* mucociliary processes and swallowing. See further discussion in the following bullets.
- The contribution to Mn levels in the brain from larger Mn particles (larger than PM_{10}) that are inhaled and removed from the respiratory tract *via* mucociliary processes and then swallowed would be very small compared to that ingested from the diet. That is, if one assumes, as a hypothetical, a total Mn concentration of 50 µg/m^3 with 80% consisting of particulate matter larger than PM_{10} (*i.e.*, 40 µg/m^3) and 20%[6] consisting of respirable particulate matter (PM_{10}) (*i.e.*, 10 µg/m^3), an inhalation rate of 20 m^3/day (US Environmental Protection Agency [US EPA] daily inhalation rate for the general population; US EPA, 2011), and that all of the larger particles are ingested, the ingested amount is only about 4-27% of what is normally ingested in the diet (3-20 mg/day) (IOM, 2001). The calculation is as follows: 40 µg/m^3 × 20 m^3/day = 800 µg/day (which is 27% of 3,000 µg/day and 4% of 20,000 µg/day). Note that this is overly conservative for East Liverpool, Ohio, because it assumes a Mn total suspended particulate (TSP) concentration of 50 µg/m^3, which is much greater than monthly and annual average Mn TSP concentrations measured in this community (US EPA, 2017).
- A value 27% above the normal level of Mn in the brain (0.4 µg/g) is approximately 0.5 µg/g, which is still well below the NOEL of 0.8 µg/g Mn in the brain estimated by Schroeter *et al*. (2012).

[4] Micrometer = Micron.
[5] Mass median aerodynamic diameter (MMAD). An MMAD of 2-3 microns also includes particles smaller than 2-3 microns.
[6] Based on a comparison of annual average Mn TSP and PM_{10} data from the East Liverpool, Ohio Water Plant Monitoring Station in 2009.

- If one performs the same calculation as above but with the highest monthly average TSP Mn concentration measured in East Liverpool, Ohio, from 2013-2016 (5.99 µg/m^3 at the Water Treatment Plant Monitoring Station in September 2014) (US EPA, 2017) and compares that to the average PM_{10} data collected during the same month at the same monitoring station (0.91 µg/m^3), an estimated amount of Mn in air that could be swallowed (particles larger than PM_{10}) is 5.08 µg/m^3 (5.99 µg/m^3 – 0.91 µg/m^3 = 5.08 µg/m^3). The calculation is then 5.08 µg/m^3 × 20 m^3/day = 102 µg/day, which is 0.5-3.4% of what is normally ingested in the diet and would not result in an increase in Mn above normal levels in the brain.

3.4 Recommendations for Revised Monthly Response Action Levels

Taken together, the best available science suggests that an Exceptional Action Level of 10 µg/m^3 respirable Mn in air would be sufficiently health protective and well below Mn concentrations in air that are likely to lead to increased levels of Mn in the brain (*via* Mn in the diet, inhalation and distribution of Mn through the bloodstream and olfactory nerve, and ingestion of larger Mn particles that might be coughed up from the lungs and swallowed).[7]

[7] Note that, based on our analysis presented herein, the current calendar monthly average Preventative Action Level of 0.57 µg/m^3 PM_{10} Mn is also overly conservative and well below levels that would lead to adverse health effects from Mn exposure.

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Appendix A

Review of the Manganese (Mn) Ambient Air Concentrations Near the SH Bell Facility in East Liverpool, Ohio Described by ATSDR Region 5 in Their September 22, 2016, Letter

GRADIENT

October 24, 2016

Michelle Colledge, Ph.D., M.P.H.
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Agency for Toxic Substances and Disease Registry
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Re: Review of the Manganese (Mn) Ambient Air Concentrations Near the SH Bell Facility in East Liverpool, Ohio Described by ATSDR Region 5 in their September 22, 2016 Letter

Dear Dr. Colledge:

Gradient has reviewed the recent letter prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) Region 5 regarding manganese (Mn) air concentrations in the vicinity the SH Bell facility in East Liverpool, Ohio ("the SH Bell facility" herein) (ATSDR, 2016a). The letter, dated September 22, 2016, describes potential risks from Mn measured at seven air monitoring stations near the SH Bell facility (Water Plant, Maryland Ave, Port Authority, Chester, Lawrenceville, Glasgow, and Midland) from 2005-2016.

The results of our review are summarized below:

1. For evaluating potential human health risks from Mn in air, ATSDR should use only the Mn Minimal Risk Level (MRL), a value that is supported by the best available science, and not the outdated US EPA Mn reference concentration (RfC).
2. ATSDR's comparison of total suspended particulate (TSP) Mn concentration data to the Mn MRL is not scientifically supported. Instead, ATSDR should have used the more biologically appropriate respirable or PM_{10} (particulate matter with size mostly 10 microns or less)[1] Mn concentration data for comparison to the MRL.
3. The Mn PM_{10} data available to date for East Liverpool, OH suggest that Mn PM_{10} concentrations are only 20-35% of the Mn TSP air concentrations. Therefore, Mn TSP concentrations are not a reliable indicator of the more biologically appropriate respirable or PM_{10} Mn concentrations, and use of Mn TSP data results in a larger and incorrect estimate of Mn risk for the East Liverpool community than would be obtained from the Mn PM_{10} data. It is our understanding that ATSDR is aware of Mn PM_{10} data for East Liverpool for 2009 and of the difference in PM_{10} *vs*. TSP Mn concentrations, and we have been informed that they are also aware of 2016 Mn PM_{10} data; therefore, it is unclear why ATSDR used Mn TSP data instead of the more biologically relevant Mn PM_{10} data to evaluate Mn risk for the East Liverpool community.
4. ATSDR's use of daily or average monthly Mn concentrations for comparison to the MRL is not scientifically supported. Instead, ATSDR should have only compared long-term chronic average Mn concentrations to the MRL.

[1] Note that PM_{10} is generally a conservative estimate of the concentration in the respirable PM_5 fraction.

5. Our evaluation of more recent Mn PM_{10} data, and application of long-term average exposure concentrations, indicates there is no exceedance of the Mn MRL, and, therefore, no increased risk from Mn to the East Liverpool, OH community.
6. Two recent community studies incorrectly concluded, based on comparisons of Mn TSP data for East Liverpool, OH *vs*. Marietta, OH, that there is a correlation between an increase in neurological deficits in the East Liverpool community and increased levels of Mn in air. However, comparison of the more biologically relevant Mn PM_{10} data to health indicators between these two towns does not provide reliable evidence for a correlation between neurological effects and levels of Mn in air in East Liverpool.
7. Therefore, there is no scientific basis for ATSDR's conclusions that Mn exposures in the East Liverpool community represent a public health hazard and that such exposures should be mitigated as soon as possible to reduce harmful exposures.

The following section describes our analysis in more detail.

Evaluation of ATSDR's Mn Risk Assessment Approach

Mn Toxicity Criteria

We commend ATSDR for referring to the ATSDR MRL for Mn of 0.3 $\mu g/m^3$ (ATSDR, 2012). However, it is unclear why ATSDR also refers to the outdated US EPA Mn RfC of 0.05 $\mu g/m^3$ (US EPA, 2002). ATSDR should only compare Mn air concentrations to their own value (the MRL) that is based on the most current available science on Mn toxicity, and applies US EPA's current benchmark dose modeling for derivation of the value.

US EPA's Integrated Risk Information System (IRIS) RfC for Mn (0.05 $\mu g/m^3$) was derived in 1993 and has not been reviewed or updated in more than 20 years. This RfC is based on observations of subclinical neurological effects in workers exposed to Mn for an average of 5.3 years (Roels *et al*., 1992). Based on an 8-hour time-weighted average (TWA), the geometric mean exposure in the battery workers, 150 $\mu g/m^3$ respirable Mn, was considered the lowest observed adverse effect level (LOAEL). US EPA calculated a human equivalent concentration LOAEL ($LOAEL_{[HEC]}$) of 50 $\mu g/m^3$, which accounted for differences in exposure duration between workers and the general population. US EPA applied a total uncertainty factor (UF) of 1,000 to the $LOAEL_{[HEC]}$ to account for sensitive populations (UF = 10), use of a LOAEL instead of a no observed adverse effect level (NOAEL) (UF = 10), as well as database limitations, subchronic exposure, and potential differences in the toxicity of different forms of Mn (UF = 10), resulting in an RfC of 0.05 $\mu g/m^3$. Many studies conducted after 1993 suggest that revision to the Mn RfC is in order.

The ATSDR MRL for Mn (ATSDR, 2012) is based on the same occupational study as the US EPA Mn RfC (Roels *et al*., 1992), but ATSDR considered more recent Mn studies to develop their MRL, including pharmacokinetic studies that describe the distribution of inhaled Mn to the brain (Andersen *et al*., 2010; Schroeter *et al*., 2011; Yoon *et al*., 2011). ATSDR applied US EPA's most recent Benchmark Dose (BMD) Software to derive a $BMCL_{10}$ (95% lower confidence limit on the BMD for a 10% extra risk compared to controls) and a point of departure (POD) of 142 $\mu g/m^3$ for abnormal eye-hand coordination in workers exposed to respirable Mn in the Roels *et al*. (1992) study. ATSDR adjusted the 142 $\mu g/m^3$ POD to account for continuous exposure in the general population (*vs*. a worker population) (142 $\mu g/m^3$ × 5/7 days/week × 8/24 hours/day = 34 $\mu g/m^3$), and applied a UF of 10 for limitations/uncertainties and another UF of 10 for human variability, for a total UF of 100, resulting in an MRL of 0.3 $\mu g/m^3$. Because of the many studies conducted since 1993 that address some of the uncertainties in the 1993 Mn RfC,

fewer UFs were needed to derive the MRL, resulting in a value that is more scientifically supported and six-fold higher than the existing US EPA Mn RfC.

It is important to note that both the ATSDR MRL and US EPA RfC Mn values are very conservative. Exceedance of these values does not mean that a health effect will occur. For example, the Mn ATSDR MRL (ATSDR, 2012) is based on a no observed effect level (NOEL) of 142 µg/m^3 from a worker manganese exposure study that was adjusted to a continuous exposure NOEL of 33 µg/m^3, and then further adjusted with a 100-fold uncertainty factor applied for sensitive populations.

Further, peer-reviewed studies suggest that Mn brain concentrations would not exceed normal levels in adults, children, neonates, and fetuses at Mn exposure concentrations as high as 10 µg/m^3 (Schroeter *et al*., 2011; Yoon *et al*., 2011; Schroeter *et al*., 2012), providing further support for the conservatism of the Mn MRL of 0.3 µg/m^3.

Recent Application of the Mn MRL by US EPA, ATSDR, and the State of Michigan

The following statements summarize recent agency application of the Mn MRL instead of the Mn RfC for evaluating Mn risk (including US EPA offices and ATSDR).

- US EPA's Office of Air Quality Planning and Standards (OAQPS) lists the ATSDR Mn MRL, and not the Mn RfC, on its summary table of dose-response values for screening level air risk assessments (US EPA, 2016a).
- US EPA's OAQPS recently applied the Mn MRL, and not the Mn RfC, to evaluate air Mn risk in the National Emissions Standards for Hazardous Air Pollutants (NESHAP) Ferroalloys Production Final Rule (US EPA, 2015). US EPA considered public comments on earlier drafts of the rule regarding use of the Mn RfC as not being consistent with the best available science. In consideration of these comments, US EPA states in the final rule that:

  > "After considering the values in our tiered list of prioritized dose-response values, and consistent with Agency policy supported by SAB, we decided to rely on the 2012 ATSDR MRL value for the 2014 supplemental proposal. Both the 1993 IRIS RfC and the 2012 ATSDR MRL were based on the same study (Roels *et al*., 1992). In developing their assessment, ATSDR used updated dose response modeling methodology (benchmark dose approach) and considered recent pharmacokinetic findings to support their selection of uncertainty values in the MRL derivation." (p. 37375, US EPA, 2015).

- US EPA's Office of Air and Radiation (OAR), of which OAQPS is a part, recently updated their summary of Mn toxicity and health risk values as part of their "Health Effects Notebook for Hazardous Air Pollutants" (US EPA, 2016b). This summary no longer includes the Mn RfC, but does list the Mn MRL.
- US EPA's recent report on the environment for Mn concentrations in EPA Region 5 refers only to the ATSDR Mn MRL and not to the US EPA Mn RfC (US EPA, 2014). The report indicates that Mn PM_{10} data are most appropriate for comparison to the MRL, but that only Mn TSP data were available; the report also states that TSP Mn data will result in a "conservative estimate of risk" (see further discussion below regarding Mn TSP *vs*. PM_{10} data[2]). The report shows that although TSP data represent a conservative estimate, most of the Mn TSP annual average concentrations in

[2] Note that PM_{10} is generally a conservative estimate of the concentration in the respirable PM_5 fraction.

EPA Region 5 were below the MRL of 0.3 μg/m^3, indicating that the Mn PM_{10} data would be well below the MRL[3].

- ATSDR recently applied the Mn MRL, and not the Mn RfC, in its Health Consultation for the Koch Carbon, LLC ("KCBX") "Chicago Petroleum Coke" site in Chicago, Cook County, Illinois (ATSDR, 2016b). ATSDR's use of both the Mn RfC and the Mn MRL, and not just the Mn MRL, in its more recent letter regarding East Liverpool, OH is inconsistent with their KCBX "Chicago Petroleum Coke" Health Consultation. Note that ATSDR's KCBX "Chicago Petroleum Coke" Health Consultation was dated August 22, 2016, one month prior to the September 22, 2016 letter referred to here.
- The Michigan Department of Environmental Quality (MDEQ) lists the Mn MRL as its Initial Threshold Screening Level (ITSL) for Mn air risk assessment, and specifies that the value should be compared to annual average PM_{10} Mn concentrations (MDEQ, 2016).

ATSDR's Use of TSP Rather than Respirable or PM_{10} Mn Air Data

ATSDR's use of TSP rather than respirable or PM_{10} Mn air data does not reflect the best available science. The Mn RfC and MRL were derived from a study of workers in which Mn exposures were quantified using the respirable fraction of Mn particulates in air (Roels *et al*., 1992; ATSDR, 2012). The respirable fraction represents the fraction of Mn particulates which can penetrate to the deep lung and be absorbed systemically. In contrast, larger particulates are trapped in the upper airways, *i.e.* the naso-pharyngeal passages, and do not penetrate the lung tissue, and thus, are not absorbed systemically. For evaluation of potential health risks from Mn, it is therefore scientifically appropriate to use the respirable particulate fraction of Mn in air, and not the TSP Mn fraction. In fact, on page 7 of their letter, ATSDR recognizes that the Mn MRL is based on the respirable fraction, but they provide no rationale for why they then compare the Mn TSP data to the Mn MRL.

Use of Mn TSP instead of Mn PM_{10} data is particularly problematic for East Liverpool, OH where Mn PM_{10} concentrations are only 20-35% of Mn TSP concentrations (Colledge *et al*., 2015; Ohio EPA 2010)[4]; in this case, use of TSP data results in an incorrect and largely overestimated Mn risk for the East Liverpool community. Dr. Michelle Colledge, the author of the September 22, 2016 ATSDR letter to which our comments here refer, is also the first author of the Colledge *et al*. (2015) article. It is puzzling that Dr. Colledge does not refer to her own 2015 Mn exposure analysis in the letter, especially since the analysis demonstrates that Mn PM_{10} is a relatively small contributor to TSP Mn in the East Liverpool Community. Despite the availability of both PM_{10} and TSP Mn modeled concentrations in East Liverpool, OH, additional studies that attempted to correlate Mn air concentrations with neurological effects in the community (Bowler *et al*., 2015, 2016)[5] incorrectly used TSP and not PM_{10} Mn data.[6] The authors do not discuss why they used TSP rather than the scientifically appropriate PM_{10} Mn concentrations.

In addition, we were recently made aware that Ohio EPA collected Mn PM_{10} data from the Water Plant monitoring station from January 2015 through August 2016 (Ohio EPA, 2015, 2016). We have been informed that ATSDR is aware of 2016 Mn PM_{10} data, and it is our understanding that they are also

[3] Given that US EPA's air offices (OAQPS and OAR) recommend and apply the Mn MRL, and not the Mn RfC, for Mn air risk evaluations, it is not clear why US EPA still refers to the outdated Mn RfC on its IRIS database (US EPA, 2002).
[4] Note that the fraction of Mn PM_{10} varies depending on the source. US EPA's recent report on the environment for Mn in EPA Region 5 (2014) suggests the Mn PM_{10} fractions can range from 50 to 75%; therefore, PM_{10} levels in East Liverpool are lower than what is typically observed.
[5] Dr. Colledge is a co-author on these studies.
[6] Note that PM_{10} is generally a conservative estimate of the concentration in the respirable PM_5 fraction.

aware of 2009 Mn PM_{10} data collected by Ohio EPA from the Water Plant monitoring station (Ohio EPA, 2010). It is not clear why ATSDR did not use these data in their recent evaluation.

Further, ATSDR recently compared Mn PM_{10} data, and not Mn TSP data, to the Mn MRL in its Health Consultation for the KCBX "Chicago Petroleum Coke" site in Chicago, Cook County, Illinois (ATSDR 2016b), providing precedent for application of PM_{10} data in Mn risk evaluation.

As discussed, ATSDR provides no support for its use of only Mn TSP data. This is particularly troublesome since Mn PM_{10} monitoring data from 2009 (Ohio EPA, 2010) and 2016 (Ohio EPA, 2016), and Mn PM_{10} modeled data (Colledge *et al*., 2015), were available at the time ATSDR prepared its September 2016 letter. As a result, the statements on page 7 of the ATSDR letter that discuss Mn TSP concentrations that exceed the MRL and RfC are incorrect (both in comparison of TSP instead of PM_{10} Mn data, and in comparison to the Mn RfC). Although some of the Mn TSP concentrations do exceed the Mn MRL, conclusions regarding Mn risks should only be made *via* comparison of the MRL to the more scientifically appropriate respirable or PM_{10} Mn fraction, and only *via* comparison to exposure concentrations of one year or more (see further discussion below).

ATSDR's Comparison of the MRL to Daily and Monthly Mn Values as Opposed to Chronic Average Mn Concentrations

Instead of using the appropriate metric of long-term Mn air concentrations for comparison to the Mn MRL, ATSDR uses daily and monthly average Mn air concentrations. As discussed below, this comparison results in unsupported conclusions about risk exceedances.

The Mn MRL is a chronic value as defined by ATSDR (ATSDR, 2012); as such, the document specifically states that a chronic value is based on exposures of at least one year. It is widely accepted in the scientific community that chronic toxicity values should be compared to data averaged over periods of at least one year or more. Additionally, the US EPA Risk Assessment Guidance for Superfund (RAGS) (1989) defines chronic exposure as exposure over a long period of time (*i.e.*, seven years or more), and defines chronic reference concentrations (such as an MRL) as values specifically developed to be protective for long-term exposures (*i.e.*, seven years or more). Chronic toxicity values, therefore, should be compared to long-term exposures of at least one year, and not to short-term daily or monthly values. Comparison of chronic toxicity values to monthly or daily exposure estimates is scientifically incorrect and can overstate risks.

Therefore, ATSDR's discussion on page 7 of their letter that compares monthly and daily TSP Mn data to the Mn MRL is incorrect with respect to potential risks from Mn. There is no basis for providing percent of daily exceedances of the Mn MRL since daily comparisons are incorrect. As discussed below, our evaluation of long-term average PM_{10} Mn data collected from the Water Plant monitoring station indicates there is no increased risk from Mn in the East Liverpool, Ohio community.

Evaluation of Potential Risk from Mn in Air using Mn PM_{10} Data from the Water Plant Monitoring Station

Ohio EPA collected Mn PM_{10} data from the Water Plant monitoring station from January 2015 through August 2016 (Ohio EPA, 2015, 2016). Data are shown in Tables 1 and 2.

As shown in Table 1, there were 60 Mn PM_{10} air samples collected in 2015 and 41 samples collected in 2016. The average Mn PM_{10} exposure concentration for the two years of 0.3 $\mu g/m^3$ does not exceed the

Mn MRL. These data are consistent with Mn PM_{10} data collected by Ohio EPA from the Water Plant monitoring station from January through March 2009 (average of 0.15 µg/m^3) (Ohio EPA, 2010).

As discussed above, the Mn MRL is a very conservative value, and exposure concentrations at or above this value do not mean health effects will occur. In fact, all of the values in Table 1 and Table 2 are well below the Mn air concentrations at which health effects have been confirmed in humans[7], and well below air concentrations at which Mn is modeled to begin to accumulate in the brain above normal levels (10 µg/m^3) (Schroeter *et al*., 2011; Yoon *et al*., 2011; Schroeter *et al*., 2012).

Evaluation of the Health Studies Conducted in East Liverpool, Ohio

ATSDR also discusses the recent East Liverpool, OH and Marietta, OH community studies conducted by Colledge *et al*. (2015) and Bowler *et al*. (2015, 2016) to suggest that elevated levels of Mn in air in East Liverpool are related to lower neuropsychological test scores in adult residents. This inference does not consider the relevant Mn air particulate size for drawing conclusions regarding risk and, as such, represents a scientifically inappropriate interpretation of the data. As discussed below, these studies do not provide reliable evidence of an association between elevated Mn levels and lower neuropsychological scores in East Liverpool residents.

Colledge *et al*. (2015) modeled TSP, PM_{10}, and $PM_{2.5}$ Mn concentrations for two Ohio towns (East Liverpool, OH and Marietta, OH). Colledge *et al*. (2015) used US EPA's AERMOD air dispersion model to model Mn air concentrations for each community residence point in East Liverpool and Marietta, OH. Bowler *et al*. (2015, 2016) conducted neurological tests on 100 and 86 residents in East Liverpool and Marietta, respectively (cognitive functions in Bowler *et al*. [2015] and tremor and motor function in Bowler *et al*. [2016]), and attempted to correlate neurological effects with air Mn exposure concentrations. Bowler *et al*. (2015, 2016) concluded for both studies that neurological deficits are statistically increased in adult residents in East Liverpool compared to Marietta, and that these effects are also correlated with levels of Mn in air that are higher in East Liverpool compared to Marietta. The following paragraphs describe why this conclusion is scientifically incorrect.

As described earlier, respirable Mn concentrations (which would be included in the PM_{10} fraction) represent the fraction of Mn concentrations in air that can get to the deeper parts of the lungs, be absorbed systemically, and then be transported to the brain. As such, respirable Mn concentrations are the most scientifically appropriate fraction for relating Mn exposure to potential neurological effects. Because the authors used only Mn TSP and not Mn PM_{10} data to draw conclusions regarding potential correlations with neurological effects, their conclusions regarding Mn risk are not scientifically supportable. The following table summarizes the modeled TSP, PM_{10}, and $PM_{2.5}$ Mn concentrations for each town from Colledge *et al*. (2015).[8]

[7] As discussed, ATSDR derived a NOEL for Mn of 142 µg/m^3 from a worker Mn exposure study (Roels *et al*., 1992), that was adjusted to a 24-hour/day, 7 days/week continuous exposure no effect level of 33 µg/m^3 (ATDSR, 2012).

[8] Note that the respirable fraction is typically considered PM_4 to PM_5; therefore, the $PM_{2.5}$ fraction may underestimate respirable concentrations. Since PM_4 to PM_5 data were not available, we only refer to PM_{10} concentration data for our evaluation.

Table 3 Comparison of Modeled Mn Air Concentrations in East Liverpool and Marietta, Ohio (from Colledge *et al.*, 2015)

Mn Modeled Particle Size	Estimated Average Mn Air Concentration (µg/m^3)	
	East Liverpool	Marietta
TSP	0.878	0.214
PM_{10}	0.307	0.177
$PM_{2.5}$	0.033	0.045

As shown in Table 3, PM_{10} is a much smaller fraction of TSP in East Liverpool (35%) compared to Marietta (83%). Therefore, comparisons of TSP Mn concentrations between the two towns do not reflect relative differences in the more biologically relevant respirable Mn fraction. The modeled Mn TSP average concentration for East Liverpool is about 4-fold higher than Marietta, but the Mn PM_{10} average concentrations for the two towns are similar, and both at or below the Mn MRL. Given the similarity in Mn PM_{10} air concentrations between the two towns, it is unlikely that Mn exposure explains the difference in neurological effects between the two towns.

Had the authors evaluated only the more biologically relevant Mn PM_{10} concentrations, the conclusions from these studies likely would have been different. The differences in neuropsychological effects could very well be explained by other risk factors, such as difference in education levels, which were significantly different, with educational attainment being lower in East Liverpool than in Marietta (Bowler *et al*., 2015, 2016). The authors provide no explanation as to why they used modeled TSP concentrations when modeled PM_{10} concentrations were available.

Further, all values in Table 3 are well below air concentrations at which Mn is modeled to begin to accumulate in the brain above normal levels (10 µg/m^3) (Schroeter *et al*., 2011; Yoon *et al*., 2011; Schroeter *et al*., 2012), providing further support that levels of Mn in air in these communities would not lead to adverse neurological effects.

Sincerely,

GRADIENT

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Tables

Table 1 East Liverpool Manganese PM_{10} Data from the Water Plant Monitoring Station (OhioEPA, 2015)

Month	Sample Date	Sample #	Manganese
January	06-Jan-15	195316	0.079
	12-Jan-15	195317	0.21
	18-Jan-15	195318	0.053
	24-Jan-15	195319	0.04
	30-Jan-15	195320	0.031
February	05-Feb-15	195322	0.043
	11-Feb-15	195323	0.15
	17-Feb-15	195324	0.096
	23-Feb-15	195325	0.050
March	01-Mar-15	195327	0.12
	07-Mar-15	195328	0.76
	13-Mar-15	195329	0.041
	19-Mar-15	195330	1
	25-Mar-15	195331	0.27
	31-Mar-15	195332	0.28
April	06-Apr-15	195334	0.93
	12-Apr-15	195335	0.096
	18-Apr-15	195336	0.17
	24-Apr-15	195337	0.19
	30-Apr-15	195338	0.20
May	06-May-15	195340	0.43
	12-May-15	195341	0.023
	18-May-15	195342	0.18
	24-May-15	195343	0.23
	30-May-15	195344	0.059
June	05-Jun-15	195346	0.14
	11-Jun-15	195347	0.047
	17-Jun-15	195348	1.5
	23-Jun-15	195349	0.31
	29-Jun-15	195350	0.099
July	05-Jul-15	195352	0.036
	11-Jul-15	195353	0.036
	17-Jul-15	195354	0.88
	23-Jul-15	195355	0.79
	29-Jul-15	195356	0.16
August	04-Aug-15	195358	0.064
	10-Aug-15	195359	2.6
	16-Aug-15	195360	0.033
	22-Aug-15	195361	0.13
	28-Aug-15	195362	0.25
September	03-Sep-15	195364	0.076
	09-Sep-15	195365	0.16
	15-Sep-15	195366	0.13
	21-Sep-15	195367	0.21
	27-Sep-15	195368	1.1
October	03-Oct-15	195370	0.84
	09-Oct-15	195371	2.0
	15-Oct-15	195372	0.40
	21-Oct-15	195373	0.26

Month	Sample Date	Sample #	Manganese
	27-Oct-15	195374	3.4
November	02-Nov-15	195376	0.28
	08-Nov-15	195377	0.10
	14-Nov-15	195378	<0.015
	20-Nov-15	195379	0.21
	26-Nov-15	195380	0.65
December	02-Dec-15	195382	0.049
	08-Dec-15	195383	0.23
	14-Dec-15	195384	0.14
	20-Dec-15	195385	0.29
	26-Dec-15	195386	0.049

Table 2 East Liverpool Manganese PM_{10} Data from the Water Plant Monitoring Station (OhioEPA, 2016)

Month	Sample Date	Sample #	Manganese
January	1-Jan-16	195298	0.52
	7-Jan-16	195299	<0.015
	13-Jan-16	195300	0.017
	19-Jan-16	195301	0.5
	25-Jan-16	195302	1.1
	31-Jan-16	195303	0.021
February	6-Feb-16	195305	0.032
	12-Feb-16	195306	0.072
	18-Feb-16		
	24-Feb-16	195307	0.16
March	1-Mar-16	195309	0.26
	7-Mar-16	195310	0.16
	13-Mar-16	195311	<0.016
	19-Mar-16	195312	0.015
	25-Mar-16	195313	<0.015
	31-Mar-16	195314	0.083
April	6-Apr-16	187239	0.52
	12-Apr-16	187240	0.054
	18-Apr-16	187241	0.34
	24-Apr-16	187242	0.025
	30-Apr-16	187243	0.032
May	6-May-16	188163	0.56
	12-May-16		
	18-May-16	188164	0.2
	24-May-16	188165	0.045
	30-May-16	188166	0.021
June	5-Jun-16	191135	<0.016
	11-Jun-16	191136	0.019
	17-Jun-16	191137	0.17
	23-Jun-16	191138	0.03
	29-Jun-16	191139	0.026
July	5-Jul-16	192669	<0.016
	11-Jul-16	192670	0.14
	17-Jul-16	192671	<0.016
	23-Jul-16	192672	<0.016
	29-Jul-16	192673	<0.016
August	4-Aug-16	194782	0.17
	10-Aug-16	194783	0.33
	16-Aug-16	194784	<0.016
	22-Aug-16	194785	0.041
	28-Aug-16	194786	<0.016